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PATENT SPECIFICATION (11) 1 510 054

(21) Application No. 3078/76 (22) Filed 27 Jan. 1976
(31) Convention Application No. 544 154
(32) Filed 27 Jan. 1975
(31) Convention Application No. 638 722
(32) Filed 8 Dec. 1975 in
(33) United States of America (US)
(44) Complete Specification published 10 May 1978
(51) INT CL² C07C 47/26, 43/14, 69/73, 103/58; C07D 311/72; C07F 7/02
(52) Index at acceptance
C2C 1673 200 201 202 20Y 213 21X 220 226 227 22Y 237 248 253 25Y 294 295 302 304 30Y 314 31Y 326 339 350 360 361 362 364 366 367 368 36Y 395 39Y 402 409 40Y 43X 440 46Y 490 491 49X 500 503 504 506 509 50Y 561 607 609 60X 60Y 618 623 624 628 62Y 652 672 67Y 770 771 772 778 CV CW MB QG QJ TJ WE YA YB YC YD YL
C2V 9

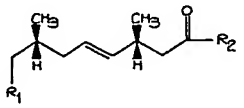
(19)

(54) CARBONYL COMPOUNDS

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to carbonyl compounds. More particularly, the invention is concerned with carbonyl compounds and a process for the manufacture thereof.

The carbonyl compounds provided by the present invention have the following general formula



(I)

wherein R_1 represents an ether group or a silyloxy group which can be converted into a hydroxy group and R_2 represents a hydrogen atom or a lower alkoxy, tri(lower alkyl)-silyloxy or di(lower alkyl)amino group.

The aforementioned ether groups include all ether groups which can be converted by hydrolysis or hydrogenolysis into the hydroxy group. Examples of such ether groups are the tetrahydropyranyloxy group, the 4 - methyl - 5,6 - dihydro - 2H - pyranyloxy group, the benzyloxy group, the benzhydryloxy group, the trityloxy group, an α - (lower alkoxy) - (lower alkoxy) group such as the methoxymethoxy group, the allyloxy group and the tert.butyloxy group. The trimethylsilyloxy group is also suitable.

Examples of compounds of formula I include 8 - tert.butoxy - 3(R),7(R) - dimethyl - oct - 4(trans) - en - 1 - oic acid ethyl ester and 8.tert.butoxy - 3(R),7(R) - dimethyl - oct - 4(trans) - en - 1 - al.

The hydrolytic conversion of the ether group denoted by R_1 into the hydroxy group can be carried out in a conventional manner by treatment with strong or weak organic or inorganic acids; for example, with lower alkanecarboxylic acids such as acetic acid or trifluoroacetic acid, with arylsulphonic acids such as p-toluenesulphonic acid or with mineral acids such as sulphuric acid or a hydrohalic acid. The acid-catalysed hydrolysis is carried out in aqueous media or in an organic solvent. When an organic acid is used, it can itself function as the solvent. The tert.butoxy group is generally hydrolysed in the presence of an organic acid which itself acts as the solvent. The tetrahydropyranyloxy group is generally hydrolysed in an aqueous medium.

The temperature and pressure are not critical. The hydrolysis can generally be carried out at room temperature and under normal pressure.

Preferred hydrolytically cleavable ether groups are the tert.butoxy group and the tetrahydropyranyloxy group.

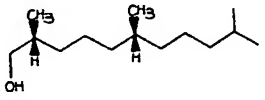
The hydrogenolytical conversion of the ether group denoted by R_1 into the hydroxy group is carried out with the aid of a hydrogenation catalyst conventionally used for this purpose; for example, with the aid of palladium or platinum. The hydrogenolysis is carried out under generally known conditions.

Preferred hydrogenolytically cleavable ether groups are the aryl-methoxy groups, especially the benzyloxy group.

The aforementioned lower alkyl groups are straight-chain and branched-chain hydrocarbon groups containing up to 7 carbon atoms. Examples of such groups are the methyl, ethyl, propyl and isopropyl groups. The aforementioned lower alkoxy groups likewise contain up to 7 carbon atoms such as, for example, the methoxy, ethoxy, propoxy and isopropoxy groups. The halogen atom can be a fluorine, chlorine, bromine or iodine atom. The alkali metal denoted by Me is sodium, potassium or lithium.

The term "cis", or the designation Δ, indicates that the two largest groups linked with the double-bond are present on the same side of the double-bond. The term "trans", or the designation Δ′, indicates that the two largest residues linked with the double-bond are present on opposite sides of the double-bond. The designation ▼ indicates that the hydrogen atom or substituent attached in place thereof lies above the plane of the paper.

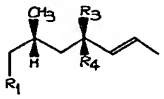
The carbonyl compounds of formula I are key intermediates for the synthesis of the optically active C_{14}-alcohol of the following formula



(IV)

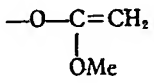
which can be condensed, as described hereinafter, with the corresponding optically-active chromane component to give the natural optically-active 2R,4′R,8′R-α-tocopherol.

According to the process provided by the present invention, the carbonyl compounds of formula I hereinbefore are manufactured by reacting an optically-active isomer of the general formula

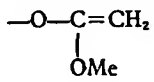


(II)

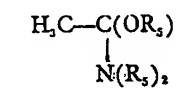
wherein R_1 is as defined above and one of R_3 and R_4 represents a hydrogen atom and the other represents the hydroxy group or the



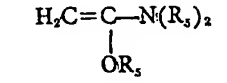
group [Me=alkali metal]; the double-bond having the cis-configuration when R_3 represents the hydroxy group or the



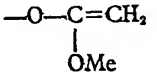
group and having the trans-configuration when R_3 represents a hydrogen atom, with an orthoacetic acid ester of the formula $H_3C—C(OR_5)_3$ [R_5=lower alkyl], a ketalised N-di(lower alkyl)-acetamide of the formula



(e.g. 1 - dimethylamino - 1,1 - dimethoxy - ethane)$_2$, an alkoxy-vinyl-dialkylamine of the formula

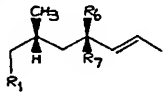


or an alkyl-vinyl ether of the formula $H_2C=CHOR_5$ (e.g. ethyl-vinyl ether) when R_3 or R_4 represents the hydroxy group or with a trialkylsilyl halide of the formula $XSi(R_5)_3$ [X=halogen] (e.g. tert.butyl-dimethyl-silyl chloride) when R_3 or R_4 represents the



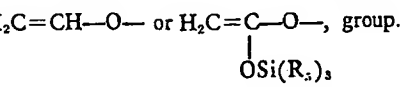
group, and subjecting the reaction product obtained to a Claisen rearrangement.

The conversion of a starting material of formula II hereinbefore into a carbonyl compound of formula I proceeds via a vinyl ether of the general formula



(III)

wherein R_1 has the significance given earlier and one of R_6 and R_7 represents a hydrogen atom and the other represents a



group.

The aforementioned Claisen rearrangement can be carried out using procedures which are known from the literature [Hill et al, J. Org. Chem. 37 (1972) 3737—3740; Sucrow et al, Chem. Ber. 104 (1971) 3689—3709 and Sucrow/Richter, Chem. Ber. 104 (1971) 3679—3688].

When an alkyl-vinyl ether of the formula $H_2C=CH—OR_5$ is used for the reaction with the starting material of formula II to yield an intermediate of formula III which is capable of undergoing Claisen rearrangement, then the

reaction is preferably carried out at a temperature between 40°C and 150°C. The reaction is carried out in the presence of any conventional acid catalyst of which inorganic acids (e.g. phosphoric acid or a hydrohalic acid) as well as acid salts (e.g. mercuric acetate) are preferred. Organic acid catalysts (e.g. p-toluenesulphonic acid and p-nitrophenol) can also be used. The reaction can be carried out in an inert organic solvent. Any such solvent having a boiling point above 40°C can be used. The preferred organic solvents are high-boiling hydrocarbons (e.g. benzene, toluene, xylene and heptane), dimethoxyethane, diethyleneglycol dimethyl ether and dioxane. The resulting vinyl ether of formula III in which one of R_6 and R_7 represents hydrogen and the other represents the $H_2C=CH-O-$ group can be converted into the desired aldehyde of formula I in which R_2 represents a hydrogen atom by simple heating to 80°—200°C.

When an orthoacetic acid ester of the formula $H_3C-C(OR_5)_3$ is reacted with a starting material of formula II, under the usual reaction conditions which are used for the Claisen rearrangement, a vinyl ether of formula III is formed initially in which one of R_6 and R_7 represents a hydrogen atom and the other represents the

$$H_2C=C(OR_5)-O-$$

group. This reaction is generally carried out using an excess of the aforementioned orthoacetic acid ester at a temperature between 140°C and 250°C. The orthoacetic acid ester can assume the function of the solvent in this reaction. The reaction can, however, also be carried out in an inert organic solvent which boils above 140°C. It is preferred to add to the reaction mixture a lower alkanecarboxylic acid in a molar amount of about 1—10% per mol of the starting material of formula II. In this manner there is obtained an alkyl ester of formula I in which R_2 represents an alkoxy group.

When a starting material of formula II is reacted with a trialkyl-silyl halide of the formula $XSi(R_5)_3$ under conditions for a Claisen rearrangement, there is initially obtained a vinyl ether intermediate of formula III in which one of R_6 and R_7 represents a

$$H_2C=C(OSi(R_5)_3)-O-$$

group. The required starting material is conveniently prepared by reacting a compound of formula II in which one of R_3 and R_4 represents a hydrogen atom and the other represents a hydroxy group with a reactive acetic acid derivative (e.g. a halogenated acetic acid or acetic anhydride), enolising the resulting acetal with the aid of an alkali metal alkylamide, the alkyl group of which can be a lower alkyl group and/or a cycloalkyl group containing 5—7 carbon atoms, preferably lithium isopropyl cyclohexylamide or lithium diisopropylamide.

The Claisen rearrangement is preferably carried out in an inert organic solvent and at a temperature between −10°C and −110°C. Any inert organic solvent which does not freeze in the aforementioned temperature range can be used, the preferred solvents being tetrahydrofuran, diethyl ether, dioxane and dimethoxyethane.

The conversion of the vinyl ether intermediate of formula III into the desired silyl ester of formula I is carried out by simple warming of the reaction mixture to 0—40°C. The vinyl ether intermediate of formula III need not be isolated from the reaction mixture prior to the conversion to the desired silyl ester of formula I. However, the vinyl ether intermediate of formula III can be isolated if desired and subsequently converted by warming into the desired silyl ester of formula I in which R_2 represents a tri(lower alkyl)-silyloxy group.

When a ketalised N-dialkyl-acetamide of the formula

$$H_3C-C(OR_5)_2-N(R_5)_2$$

or an alkoxy-vinyl-dialkylamine of the formula

$$H_2C=C(OR_5)-N(R_5)_2$$

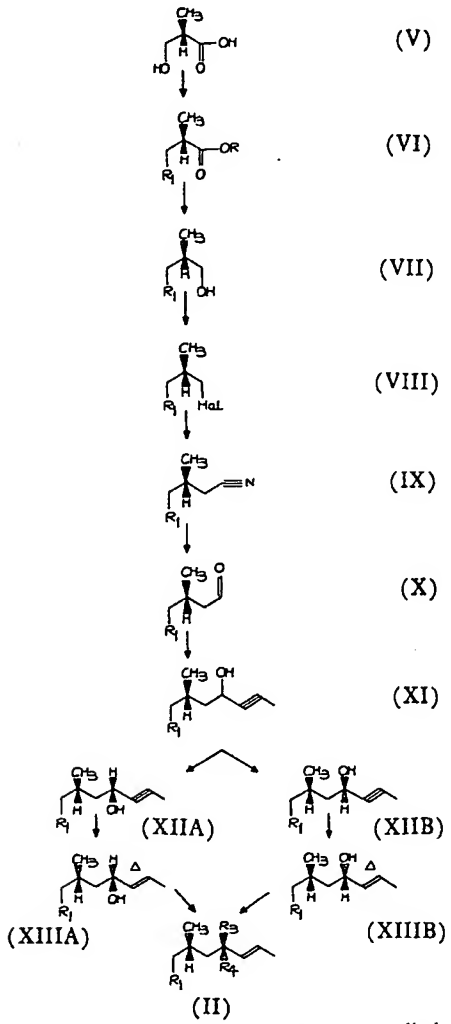
is reacted with a starting material of formula II, then the reaction conditions which are customary in Claisen rearrangements can be used. The thereby obtained vinyl ether intermediate of formula III in which one of R_6 and R_7 represents a hydrogen atom and the other represents the

$$H_2C=C(N(R_5)_2)-O-$$

group is converted immediately into the desired amide of formula I. The reaction is carried out at a temperature between 120°C and 250°C and in an inert organic solvent (e.g. xylene or diethyleneglycol dimethyl ether). There is obtained a dialkylamide of formula I in which R_1 represents a di(lower alkyl)amino group.

The enantiomeric alcohols of formula II used as the starting materials in the foregoing process can be prepared, for example, starting

from β-hydroxy-butyric acid via conventional steps as illustrated in the following Formula Scheme:



R = lower alkyl

A suitable compound for the preparation of a desired starting material of formula II is S-(+)-β-hydroxy-isobutyric acid of formula V. This acid is initially etherified and then esterified (e.g. by treatment with isobutyric acid in the presence of phosphoric acid, phosphorus pentoxide and boron trifluoride etherate). The resulting ether-ester of formula VI is reduced with the aid of lithium aluminium hydride to the ether-alcohol of formula VII which is converted into the halide of formula VIII. This halide is treated with an alkali cyanide to give the nitrile of formula IX which is reduced with the aid of diisobutyl aluminium hydride to give the ether-aldehyde of formula X. The ether-aldehyde of formula X is reacted with methylacetylene under the conditions of a Grignard reaction. The resulting mixture of (2R,4R) and (2R,4S) - 1-tert.butoxy - 2 - methyl - hept - 5 - yn - 4 - ol of formula XI is separated by preparative high-pressure/liquid chromatography into:

1 - tert.butoxy - 2(R) - methyl - hept - 5-yn - 4(S) - ol (XIIA)

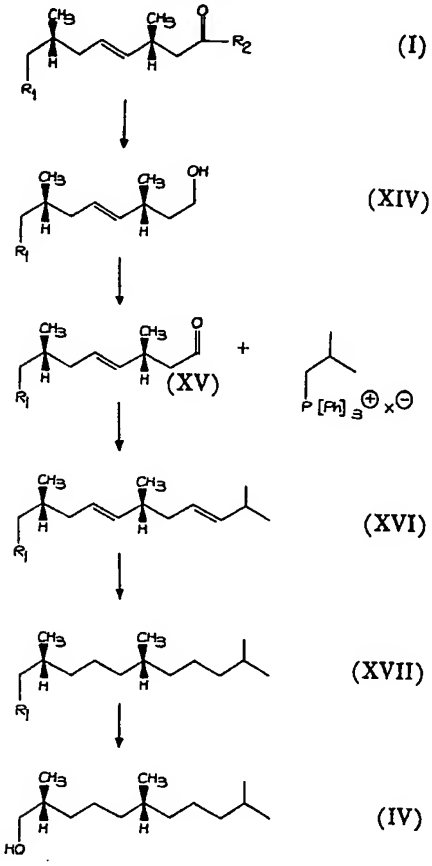
and

1 - tert.butoxy - 2(R) - methyl - hept - 5-yn - 4(R) - ol (XIIB)

The ethynyl group in the compounds of formula XIIA and XIIB is subsequently partially hydrogenated to the vinylene group. There is thereby obtained, insofar as the partial hydrogenation is carried out catalytically, i.e. with the aid of a partially deactivated noble-metal catalyst such as a Lindlar catalyst [$Pd/CaCO_3/PbO$], a vinyl carbinol of formula XIIIA or XIIIB in which the double-bond has the cis-configuration. If the reduction of the ethynyl group is carried out chemically (e.g. by treatment with sodium in liquid ammonia or with aluminium hydride), then there is obtained a vinyl carbinol of formula XIIIA or XIIIB in which the double bond has the trans-configuration.

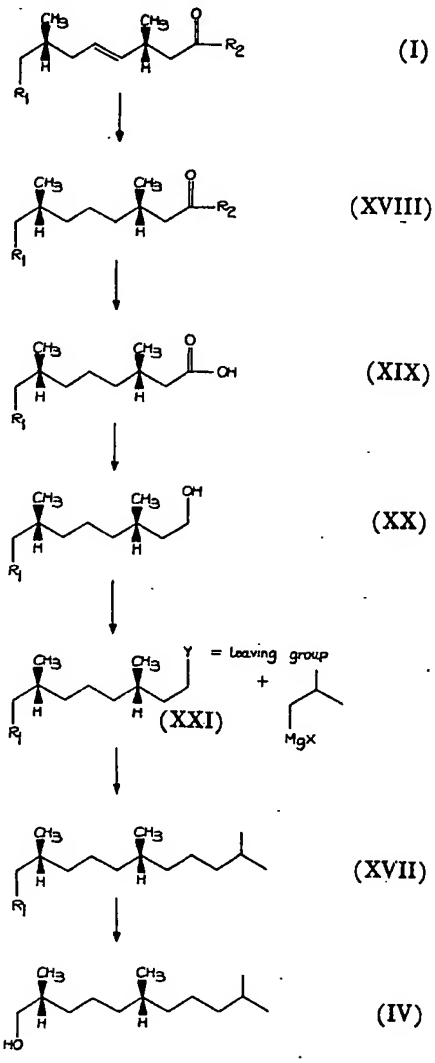
The resulting diastereomeric alcohols of formula XIIIA and XIIIB represent the starting materials for the process provided by the present invention and can be generically formulated as formula II hereinbefore.

The optically active carbonyl compounds of formula I manufactured in accordance with the process provided by the present invention from the diastereomeric alcohols of formula II by Claisen rearrangement can be converted in the manner shown in the following Formula Scheme into the previously mentioned optically active 2(R),6(R)-C_{11}-alcohol of formula IV:



A carbonyl compound of formula I can be reduced, for example, by treatment with lithium aluminium hydride, to give the corresponding alcohol of formula XIV. This alcohol is oxidised by treatment with an oxidising agent (e.g. chromium trioxide) to give the aldehyde of formula XV which is chain-lengthened by reaction with an isobutyl-triphenylphosphonium halide under the conditions of a Wittig reaction to give the C_{14}-diene of formula XVI. This diene is subsequently reduced with the aid of a noble-metal catalyst (e.g. palladium/carbon) under normal conditions to give the corresponding C_{14}-ether of formula XVII which can be converted by hydrolysis or hydrogenolysis depending on the nature of the ether group, as described earlier, into 2(R),6(R),10 - trimethyl - undecan - 1-ol, the desired optically active C_{14}-alcohol of formula IV.

The optically active carbonyl compounds of formula I can also be converted into the desired optically active 2(R),6(R) C_{14}-alcohol of formula IV in the manner shown in the following Formula Scheme:



The olefinic bond of a carbonyl compound of formula I can be hydrogenated in the presence of a metal catalyst (e.g. Raney-nickel) under normal conditions. In this manner, from an 8 - alkoxy - 3(R),7(R) - dimethyl - oct-4 - en - 1 - oic acid ester of formula I there is obtained an 8 - alkoxy - 3(S),7(R) - dimethyl - octan - 1 - oic acid ester of formula XVIII.

The resulting ester of formula XVIII is then saponified by treatment with alkali to the free acid of formula XIX which is reduced with the aid of a complex aluminium hydride (e.g. lithium aluminium hydride) to the alcohol of formula XX.

The resulting alcohol of formula XX is then

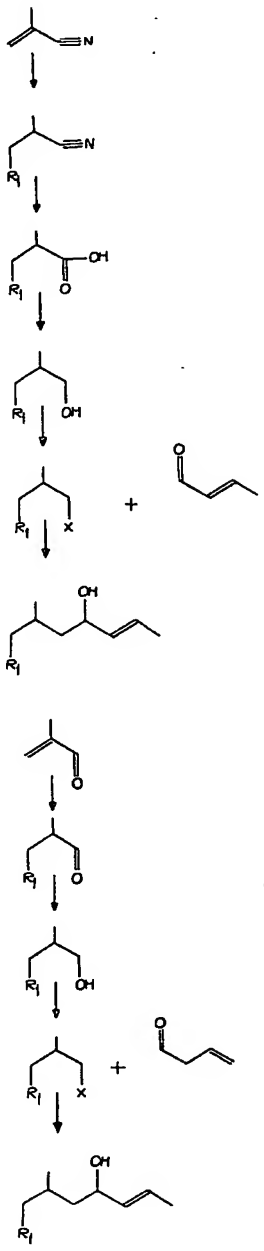
converted into a compound of formula XXI by the introduction of a leaving group. For example, the alcohol can be treated with p-toluenesulphonyl chloride to give the p-toluenesulphonate. The compound of formula XXI is then chain-lengthened with an isobutyl-magnesium halide in the presence of a di(alkali metal) - tetrahalocuprate to give the C_{14}-ether of formula XVII. In this manner, for example, a 1 - alkoxy - 3(S),7(R) - dimethyl-octan - 1 - ol p-toluenesulphonate is chain-lengthened to a 1 - alkoxy - 2(R),6(R),10-trimethyl - undecane.

The resulting C_{14}-ether of formula XVII can be converted by hydrolysis or hydrogenolysis depending on the nature of the ether group, as mentioned earlier, into 2(R),6(R), 10 - trimethyl - undecan - 1 - ol, the desired optically active C_{14} - alcohol of formula IV.

The optically active C_{14}-alcohol of formula IV obtainable from the aliphatic carbonyl compounds of formula I can be reacted with the appropriate chromane component to give optically active 2(R),4'(R),8'(R) - α - tocopherol. As described in Examples 4 and 5 hereinafter, the C_{14}-alcohol of formula IV is converted, via the bromide, into 2(R),6(R)-(−) - 2,6,10 - trimethyl - undec - 1 - yl-magnesium bromide and this is reacted in the presence of di - lithium - tetrachlorocuprate with (S) - (−) - 6 - benzyloxy - 2,5,7,8-tetramethyl - chroman - 2 - ethyl - methanesulphonate to give 2R,4'(R),8'(R) - α - tocopheryl benzyl ether which can be saponified to give 2R,4'(R),8'(R) - α - tocopherol.

The present invention provides a valuable synthesis of the optically active carbonyl compounds of formula I which, as will be evident from the foregoing, can be converted into the optically active C_{14}-alcohol of formula IV. It will be appreciated that diastereomeric mixtures of formula I manufactured from the diastereomeric mixtures of formula II yield diastereomeric mixtures of the C_{14}-alcohol of formula IV.

The diastereomeric mixture of formula II can be prepared either from a racemic β-hydroxy - butyric acid as described earlier or from methacrylonitrile 1) or methacrolein 2) as shown in the following two Formula Schemes:



When methacrylonitrile 1) is used, then this is initially converted into the ether 1a) by the addition of an alcohol. The ether 1a) is saponified, the resulting acid 1b) is reduced and the resulting alcohol 1c) is converted into a halide 1d) which can be condensed with crotonaldehyde under the conditions of a Grignard reaction to give the enantiomeric alcohol starting material of formula II.

When methacrolein 2) is used, then this is likewise initially reacted with an alcohol to give the ether 2a). This ether is reduced to the alcohol 2b) [1c] and converted into a halide 2c) [1d] which can be condensed with crotonaldehyde under the conditions of a Grignard reaction to give the enantiomeric alcohol starting material of formula II.

The enantiomeric alcohol of formula II can be converted according to the two procedures described earlier into the enantiomeric C_{14}-alcohol which, for example, after conversion into a halide, can be condensed with 6-acetoxy - 2,5,7,8 - tetramethyl - chroman - 2-ethyl - methanesulphonate in the presence of a di - (alkali metal) - tetrahalocuprate to give rac. α - tocopheryl acetate.

The following Examples illustrate the present invention:

Example 1.

34.8 mg of propionic acid in 5.3 g of orthoacetic acid triethyl ester are added to 1.1 g of 2(R),4(S) - cis - 1 - tert. - butoxy - 2-methyl - hept - 5 - en - 4 - ol and the mixture is heated while stirring in an oil-bath until distillation commences. The distillation is continued until the internal temperature reaches 150°C. The solution is subsequently heated under reflux for 3.25 hours, cooled, introduced into water and extracted with ether. The ether extract is washed with a saturated aqueous sodium chloride solution and then with a saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated under reduced pressure. The residual 3(R),7(R) - trans - 8 - tert.butoxy - 3,7 - dimethyl - oct - 4 - en - 1 - oic acid ethyl ester, a colourless oil, boils at 74°—78°C/0.2 Torr.

The 2(R),4(S) - cis - tert.butoxy - 2-methyl - hept - 5 - en - 4 - ol used as the starting material can be prepared, for example, as follows:

a) 0.91 ml of 100% phosphoric acid (prepared by dissolving 5 g of phosphorus pentoxide in 85% phosphoric acid) and 2 ml of boron trifluoride etherate are treated at −72°C to −78°C while stirring within 5 minutes with 5 g of a mixture consisting of (S) - (+) - β - hydroxy - isobutyric acid (ca 38 wt.%) and isobutyric acid (ca 55 wt.%) dissolved in 55 ml of methylene chloride. The mixture is stirred for 30 minutes at −72°C and then for 3 hours at 0°C, introduced into a solution of 5.4 g of sodium bicarbonate in 95 ml of water and extracted with methylene chloride. The extract is worked-up as described earlier. The residual oily S-(+) - 3 - tert.butoxy - 2 - methyl - propionic acid tert.butyl ester is purified by adsorption on 180 g of silica gel using hexane/ether (19:1) and (9:1) for the elution. The pure compound, a colourless liquid, boils at 77°—79°C/10 Torr; $[\alpha]_D^{25} = +19.74°$ (c=4 in methanol).

b) 1 g of S - (+) - 3 - tert.butoxy - 2-methyl - propionic acid tert.butyl ester is dissolved in 13 ml of absolute ether. The solution is treated within 5 minutes while stirring at 5°—10°C with a slurry consisting of 0.352 g of lithium aluminium hydride and 13 ml of absolute ether. The mixture is stirred for 3 hours at room temperature and then cautiously decomposed in the cold by the addition of 0.66 ml of a 10% aqueous sodium hydroxide solution. The mixture is stirred for a further 15 minutes. The precipitated solid materials are filtered off and washed with ether. The ethereal washings are combined with the filtrate, washed with a sodium chloride solution, dried and evaporated under reduced pressure. The residual R - (+) - tert.butoxy - 2 - methyl - propan - 1 - ol is purified by adsorption on 30 g of silica gel using hexane/ether (2:1) and (1:1) for the elution. The pure alcohol, a colourless liquid, boils at 62°—67°C/10 Torr; $[\alpha]_D^{25} = +0.49°$ (c=4 in methanol).

c) 19.3 g of R - (+) - tert.butoxy - 2-methyl - propan - 1 - ol and 38.6 g of triphenylphosphine are dissolved in 75 ml of methylene chloride. The solution is treated portionwise while cooling with 24.9 g of N-bromosuccinimide. In so doing, the temperature should not rise above 30°C. The mixture is stirred for 1 hour at room temperature. The methylene chloride is then removed under atmospheric pressure. The residue is distilled. The R - (+) - 3 - tert.butoxy - 2 - methyl-1 - bromo - propane which distils off is a colourless liquid boiling at 62°—65°C/10 Torr. The bromide is dissolved in 144 ml of methanol and 36 ml of water. The solution is treated with 11.67 g of sodium cyanide. The mixture is heated to boiling under reflux for 17 hours while stirring, then cooled, diluted with water and extracted with methylene chloride. The R - (+) - 4 - tert. - butoxy-3 - methyl - butyronitrile which is obtained after working-up the extract is purified by adsorption on 500 g of silica gel using hexane/ether (9:1) and (4:1) for the elution. The pure nitrile, a colourless liquid, boils at 88°—90°C/11 Torr; $[\alpha]_D^{25} = +7.41°$ (c=1.8 in benzene).

d) 5.8 g of R - (+) - 4 - tert.butoxy - 3-methyl - butyronitrile are dissolved in 290 ml of hexane. The solution is treated dropwise

while stirring at −65°C to −70°C with 22.4 ml of a 25% solution of lithium aluminium hydride in toluene. The mixture is stirred for 30 minutes at −65°C to −70°C and then for 3 hours at room temperature, treated dropwise with 2.8 ml of formic acid ethyl ester and introduced into 250 ml of a saturated aqueous ammonium chloride solution. The mixture is stirred for 20 minutes and, after the addition of 125 ml of 5 wt.% aqueous sulphuric acid, for a further 10 minutes. The aqueous phase which separates is extracted with ether. The ether extract is combined with the organic phase and the mixture is worked-up. The resulting R - 4 - tert.butoxy - 3 - methyl - butan - 1 - al, a colourless liquid, boils at 81—85°C/11 Torr.

e) 72.8 ml of a mixture consisting of a 2-M solution of n-butyllithium in hexane and 420 ml of absolute tetrahydrofuran is cooled to −50°C while stirring and treated dropwise at this temperature with 112 ml of methylacetylene. The resulting mixture is then warmed to 8°C under reflux and then stirred for 1 hour. The resulting white mass is cooled to 0°C and treated dropwise while stirring with a solution of 14 g of R - 4 - tert.butoxy-3 - methyl - butan - 1 - al in 125 ml of absolute tetrahydrofuran. The mixture is stirred at 0°C for 1 hour, then gradually warmed to 40°C, stirred for a further hour at this temperature, subsequently introduced into a saturated aqueous ammonium chloride solution and extracted with ether. The mixture isolated from the ether extract consists of (2R,4R) - 1-tert.butoxy - 2 - methyl - hept - 5 - yn - 4 - ol and (2R,4S) - 1 - tert.butoxy - 2 - methyl-hept - 5 - yn - 4 - ol. This mixture boils at 73°—76°C/0.1 Torr after purification by adsorption on silica gel using hexane/ether (2:1) and (1:1) for the elution.

f) 9.5 g of the mixture of (2R,4R)- and (2R,4S) - 1 - tert.butoxy - 2 - methyl - hept-5 - yn - 4 - ol in the ratio 1:1, obtained according to the preceding paragraph, are adsorbed on a 1200 mm × 21 mm (internal diameter) column of silica gel (20—44 μ) and separated at room temperature by means of high-pressure liquid chromatography [eluant: heptane/ethyl acetate (10:1); flow-rate 40 ml/minute; pressure 56 kg/cm²]. The mixture is added to the column in portions of 1.5 g. After one through-put, there are obtained 3.55 g of the 4(S) - epimer having a purity of 90%. The less polar 4(S) - epimer obtained is further purified by dissolving 208 mg thereof in ether and stirring the solution for 3.5 hours at room temperature after the addition of 10% aqueous silver nitrate solution. The pure 2(R),4(S)-1 - tert.butoxy - 2 - methyl - hept - 5 - yn - 4-ol (189 mg) isolated from the ether solution is a colourless oil boiling at 88°—94°C/0.15 Torr; $[\alpha]_D^{25} = 3.10°$ (c=2 in chloroform).

The more polar 4(R) - epimer requires 3 through-puts after which there are obtained 2.71 g. The 4(R) - epimer is purified by evaporative distillation. The pure 2(R),4(R)-1 - tert.butoxy - 2 - methyl - hept - 5 - yn-4 - ol, a colourless liquid, boils at 64°—67°C/0.02 Torr.

g) After the addition of 0.04 ml of quinoline, 1.04 g of the aforementioned 2(R),4(S)-1 - tert.butoxy - 2 - methyl - hept - 5 - yn-4 - ol are hydrogenated in the presence of 0.1 g of Lindlar catalyst [$Pd/CaCO_3/PbO$] under normal conditions. The hydrogenation is interrupted after the uptake of 1 equivalent of hydrogen after 40 minutes. The catalyst is filtered off and washed with hexane. The washings and filtrate are combined and evaporated under reduced pressure. The residual 2(R), 4(S) - cis - 1 - tert.butoxy - 2 - methyl - hept-5 - en - 4 - ol, a colourless liquid boils at 86°—89°C/0.15 Torr; $[\alpha]_D^{25} = -10.99°$ (c=2 in chloroform).

Example 2.

Conversion of 3(R),7(R) - trans - 8-tert.butoxy - 3,7 - dimethyl - oct - 4 - en-1 - oic acid ethyl ester into 2(R),6(R)-2,6,10 - trimethyl - undecan - 1 - ol [C_{14}-alcohol] according to method A:

a) A suspension of 0.432 g of lithium aluminium hydride in 20 ml of absolute ether is treated while stirring at 0°—5°C within 25 minutes with a solution of 1.73 g of 3(R),7(R) - trans - 8 - tert.butoxy - 3,7-dimethyl - oct - 4 - en - 1 - oic acid ethyl ester in 20 ml of absolute ether. The mixture is then stirred for 2.5 hours at room temperature and then cautiously treated, while cooling with ice, with 1.6 ml of a saturated aqueous sodium sulphate solution. The mixture is stirred for 16 hours at room temperature and then filtered. The filter-cake is washed with ether. The ether washing is combined with the filtrate and evaporated under reduced pressure. The residual 3(R),7(R) - trans - 8 - tert.-butoxy - 3,7 - dimethyl - oct - 4 - en - 1 - ol is purified by absorption on 50 g of silica gel using hexane/ether (2:1, (1:1) and (1:2) for the elution.

b) 0.6 g of chromium trioxide is introduced into a solution of 1.19 g of pyridine in 15 ml of methylene chloride. The brown mixture is stirred for 15 minutes at room temperature, then treated with a solution of 0.262 g of 3(R),7(R) - trans - 8 - tert.-butoxy - 3,7 - dimethyl - oct - 4 - en - 1 - ol in 3 ml. of methylene chloride and the mixture is stirred for 15 minutes at room temperature. The methylene chloride phase is then separated. The brown sediment is washed with methylene chloride. The combined methylene chloride solutions are washed successively with aqueous

1-N sodium hydroxide, aqueous 1-N hydrochloric acid, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried, filtered and evaporated under reduced pressure. The residual 3(R),7(R) - trans - 8 - tert.butoxy - 3,7-dimethyl - oct - 4 - en - 1 - al is purified by adsorption on 10 g of silica gel using hexane/ether (9:1) and (4:1) for the elution.

c) A suspension of 1.52 g of isobutyltriphenylphosphonium bromide in 30 ml of absolute tetrahydrofuran is treated while stirring and cooling to 0°C with 1.55 ml of a solution of 3.42 mM of n-butyllithium in hexane. The solution is stirred for 10 minutes at room temperature and then treated with a solution of 0.594 g of 3(R),7(R)-trans-8-tert.butoxy-3,7-dimethyl-oct-4-en-1-al in 10 ml of absolute tetrahydrofuran. The mixture is stirred for 30 minutes at room temperature, then introduced into water and extracted with hexane. The semi-solid residue obtained after working-up the hexane extract is taken up in hexane and filtered. The filtrate is evaporated under reduced pressure. The residual 2(R),6(R)-1-tert.butoxy - 2,6,10 - trimethyl - undeca - 4,8-diene is purified by absorption on 30 g of silica gel using hexane/ether (9:1) for the elution.

d) 4.59 mg of 2(R),6(R) - 1 - tert.butoxy-2,6,10 - trimethyl - undeca - 4,8 - diene are dissolved in 25 ml of ethyl acetate and hydrogenated in the presence of 200 mg of 5% palladium/carbon under normal conditions. The hydrogenation is complete after about 4 hours. The catalyst is filtered off. The filtrate is evaporated under reduced pressure. The residual 2(R),6(R) - 1 - tert.butoxy - 2,6,10-trimethyl - undecane is converted into the free alcohol as described in paragraph e) hereinafter.

e) 7 ml of trifluoroacetic acid are added to 336 mg of 2(R),6(R) - 1 - tert.butoxy-2,6,10 - trimethyl - undecane and the mixture is stirred at 0°C for 6 hours. The mixture is then poured on to ice, neutralised by the addition of aqueous 1-N sodium hydroxide and extracted with ether. The oil remaining after working-up the ether extract is taken up in 10 ml of a 10% solution of potassium carbonate in methanol and stirred at room temperature for 1 hour. The solution is then neutralised with aqueous 1-N hydrochloric acid and extracted with ether. The 2(R),6(R)-2,6,10 - trimethyl - undecan - 1 - ol [C_{14}-alcohol] isolated from the ether extract is purified by adsorption on 10 g of silica gel using hexane/ether (9:1), (4:1) and (2:1) for the elution. The pure C_{14}-alcohol boils at 74°—78°C/0.1 Torr. $[\alpha]_D^{25} = +8.42°$ (c=2 in hexane).

Example 3.

Conversion of 3(R),7(R) - trans - 8-tert.butoxy - 3,7 - dimethyl - oct - 4 - en - 1-oic acid ethyl ester into 2(R),6(R) - 2,6,10-trimethyl - undecan - 1 - ol [C_{14}-alcohol] according to method B:

a) 1.104 g of 3(R),7(R) - trans - 8 - tert.-butoxy - 3,7 - dimethyl - oct - 4 - en - 1 - oic acid ethyl ester are hydrogenated in 30 ml of ethyl acetate in the presence of a small amount of Raney-nickel under normal conditions. The hydrogenation is interrupted after 2 hours, during which time about 1 equivalent of hydrogen is taken up. The catalyst is filtered off and washed with ethyl acetate. The combined filtrates are evaporated under reduced pressure. The residual 3(S),7(R) - 8 - tert.butoxy-3,7 - dimethyl - octan - 1 - oic acid ethyl ester, a colourless oil, boils at 80°—83°C/0.15 Torr.

b) 108 mg of 3(S),7(R) - 8 - tert.butoxy-3,7 - dimethyl - octan - 1 - oic acid ethyl ester are dissolved in 2.5 ml of methanol. After the addition of 1.5 ml of 6-N caustic soda, the solution is heated to boiling under reflux for 3 hours, then cooled and extracted with ether. The ether extract is discarded. The aqueous phase is acidified with 6-N hydrochloric acid and subsequently extracted with ether. The ether extract is washed successively with water and a saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated under reduced pressure. The residual oily 3(S),7(R) - 8 - tert.-butoxy-3,7 - dimethyl - octan - 1 - oic acid has the following rotation $[\alpha]_D^{25} = +4.26°$ (c=2 in benzene).

c) 125 mg of lithium aluminium hydride in 25 ml of ether are treated dropwise while stirring in an ice-bath with a solution of 893 mg of 3(S),7(R) - 8 - tert.butoxy - 3,7 - dimethyl - octan - 1 - oic acid in 25 ml of ether. The mixture is stirred for 4 hours at 0°C and then cautiously decomposed by the addition of 0.45 ml of a saturated aqueous sodium sulphate solution. The mixture is stirred for 19 hours at room temperature and then filtered. The filtrate is evaporated under reduced pressure. The residual 3(S),7(R) - 8 - tert.butoxy - 3,7 - dimethyl - octan - 1 - ol is purified by adsorption on 30 g of silica gel using hexane/ether (2:1) and (1:1) for the elution.

d) 640 mg of 3(S),7(R) - 8 - tert.butoxy-3,7 - dimethyl - octan - 1 - ol are dissolved at 0°C in 12 ml of pyridine. The solution is treated with 1.057 g of p - toluenesulphochloride, stirred for 17 hours at 0°C, introduced into ice-water and stirred for a further 30 minutes. The oil which separates is taken up in ether. The ether extract is washed suc-

cessively with 1-N hydrochloric acid and a saturated aqueous sodium bicarbonate solution, with water and with a saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated under reduced pressure. The residual 3(S),7(R) - 8 - tert.-butoxy - 3,7 - dimethyl - octyl - p - toluenesulphonate is a yellow oil.

e) After the addition of a crystal of iodine, 432 g of magnesium powder in 1 ml of absolute tetrahydrofuran are treated while stirring with a few drops of a solution of 2.057 g of 1 - bromo - 2 - methyl - propane in 12 ml of absolute tetrahydrofuran. When the reaction begins, the remainder of the 1 - bromo - 2-methyl - propane is added dropwise. The mixture is heated to boiling under reflux for 1 hour and then cooled to room temperature. 1.42 ml of the resulting Grignard solution are then introduced dropwise at −78°C into a solution of 437 mg of 3(S),7(R) - tert.-butoxy - 3,7 - dimethyl - octyl - p - toluenesulphonate in 2.5 ml of absolute tetrahydrofuran. After the addition of 0.058 ml of a 0.1-M solution of di - lithium - tetrachlorocuprate in absolute tetrahydrofuran, the mixture is stirred at −78°C for 10 minutes, then warmed to room temperature in the course of 2 hours and subsequently stirred for a further 18 hours. The mixture is then shaken out with 1-N sulphuric acid. The organic phase is extracted with ether. The ether extract is washed successively with water, a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated under reduced pressure. The residue is purified by adsorption on 15 g of silica gel using hexane/ether (19:1) and (9:1) for the elution. The resulting 2(R),6(R) - 1 - tert.butoxy - 2,6,10-trimethyl - undecane still contains about 20% of 3(S),7(R) - 8 - tert.butoxy - 3,7 - dimethyl - 1 - bromo - octane, but it can, however, be converted into the desired C_{14}-alcohol without further purification as described in paragraph f) hereinafter.

f) 237 mg of the aforementioned crude 2(R),6(R) - 1 - tert.butoxy - 2,6,10 - trimethyl - undecane are treated while stirring at 0°C with 4 ml of trifluoroacetic acid. The resulting solution is stirred at 0°C for 17 hours. The trifluoroacetic acid is then distilled off under reduced pressure. The residue is firstly made alkaline by the addition of a 20 wt.% solution of potassium hydroxide in methanol, then neutralised with 6-N hydrochloric acid and subsequently extracted with ether. The 2(R),6(R) - 2,6,10 - trimethyl - undecan-1 - ol isolated from the ether extract is purified by adsorption on silica gel using hexane/ether (7:3) and (6:4) for the elution. The pure optically active C_{14}-alcohol, a colourless oil, has a rotation of $[\alpha]_D^{24} = +8.15°$ (c=2 in hexane).

Example 4.

0.216 g of magnesium powder and a crystal of iodine in 2.1 ml of anhydrous tetrahydrofuran are treated dropwise while stirring with a portion of a solution of 2.07 g of (2R,6R)-(−) - 1 - bromo - 2,6,10 - trimethyl - undecane in 4.9 ml of anhydrous tetrahydrofuran and the mixture is heated to boiling under reflux. When the reaction commences, the rest of the bromo compound is added. The mixture is stirred for 1 hour and then cooled to room temperature. The solution, which contains (2R,6R) - (−) - 2,6,10 - trimethyl-undec - 1 - yl - magnesium bromide, is introduced dropwise while stirring into a mixture of 2.4 g of (S) - (−) - 6 - benzyloxy - 2,5,7,8-tetramethyl - chroman - 2 - ethyl - methanesulphonate and 4.7 ml of anhydrous tetrahydrofuran. The mixture is cooled to −72°C and, after the addition of 0.27 ml of a 0.1-M solution of di - lithium - tetrachlorocuprate $[Li_2CuCl_4]$ in tetrahydrofuran, stirred firstly for 10 minutes at −72°C, then for 2 hours at 0°C and subsequently for 24 hours at room temperature. The mixture is then shaken out with 1-N aqueous sulphuric acid and extracted with ether. The yellow oil (3.6 g) isolated from the ether extract is purified by adsorption on 200 g of silica gel using hexane for the elution. The resulting (2R,4'R,8'R)-α - tocopherol benzyl ether has a rotation of $[\alpha]_D^{25} = +0.72°$ (c=0.185 in hexane).

The (S) - (−) - 6 - benzyloxy - 2,5,7,8-tetramethyl - chroman - 2 - ethyl - methanesulphonate used in the foregoing paragraph can be prepared, for example, as follows:

4a) A 70% solution of sodium - bis(2-methoxyethoxy) - aluminium hydride in 35 ml of benzene is treated dropwise while stirring in an ice-bath with a solution of 20.55 g of (S) - (−) - 6 - benzyloxy - 2,5,7,8 - tetramethyl - chroman - 2 -acetic acid methyl ester in 50 ml of benzene and the mixture is stirred at 20°C for 80 minutes. The resulting solution is further stirred at room temperature for 2 hours, then introduced into a mixture of ice and 1-N aqueous sodium hydroxide and extracted with ether. The viscous colourless oil isolated from the ether extract is taken up in petroleum ether (boiling range 30°—60°C). The precipitated (S) - (−) - 6 - benzyloxy-2,5,7,8 - tetramethyl - chroman - 2 - ethanol melts at 55°—56°C; $[\alpha]_D^{23} = -16.21°$ (c=2.03 in chloroform).

4b) 0.5 g of (S) - (−) - 6 - benzyloxy-2,5,7,8 - tetramethyl - chroman - 2 - ethanol and 0.25 ml of methanesulphonyl chloride are dissolved in 5 ml of anhydrous pyridine. The solution is maintained at 0°C for 45 minutes, then introduced into 100 ml of ice-water and, after 15 minutes, extracted with ether. The

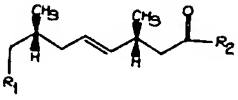
(S) - 6 - benzyloxy - 2,5,7,8 - tetramethyl-chroman - 2 - ethyl - methanesulphonate isolated from the ether extract melts at 81°—83°C; $[\alpha]_D^{25} = -0.36°$ (c = 0.82 in hexane).

Example 5.

3.55 g of (2R,4'R,8'R) - α - tocopherol benzyl ether are dissolved in 63 ml of ethyl acetate. The solution is stirred in a hydrogen atmosphere in the presence of 1.77 g of palladium/carbon (5:95). The catalyst is filtered off after completion of the hydrogen uptake. The filtrate is evaporated under reduced pressure. The residual colourless oily (2R,4'R,8'R) - α - tocopherol is converted into the acetate in the usual manner. Colourless oil; $[\alpha]_D^{25} = +3.03°$ (c = 5.1 in ethanol).

WHAT WE CLAIM IS:—

1. Carbonyl compounds of the general formula



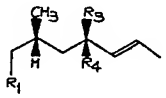
(I)

wherein R_1 represents an ether group or a silyloxy group which can be converted into a hydroxy group and R_2 represents a hydrogen atom or a lower alkoxy, tri(lower alkyl)-silyloxy or di(lower alkyl)amino group.

2. 8 - Tert.butoxy - 3(R),7(R) - dimethyl-oct - 4(trans) - en - 1 - oic acid ethyl ester.

3. 8 - Tert.butoxy - 3(R),7(R) - dimethyl-oct - 4(trans) - en - 1 - al.

4. A process for the manufacture of the carbonyl compounds of formula 1 given in claim 1, which process comprises reacting an optically-active isomer of the general formula



(II)

wherein R_1 is as defined in claim 1 and one of R_3 and R_4 represents a hydrogen atom and the other represents the hydroxy group or the

$$-O-C(=CH_2)-OMe$$

group [Me = alkali metal]; the double-bond having the cis-configuration when R_3 represents the hydroxy group or the

$$-O-C(=CH_2)-OMe$$

group and having the trans-configuration when R_3 represents a hydrogen atom, with an orthoacetic acid ester of the formula $H_3C-C(OR_5)_3$ [R_5 = lower alkyl], a ketalised N - di(lower alkyl) - acetamide of the formula

$$H_3C-C(OR_5)_2-N(R_5)_2$$

an alkoxy-vinyl-dialkylamine of the formula

$$H_2C=C(OR_5)-N(R_5)_2$$

or an alkyl-vinyl ether of the formula $H_2C=CHOR_5$ when R_3 or R_4 represents the hydroxy group or with a trialkylsilyl halide of the formula $XSi(R_5)_3$ [X = halogen] when R_3 or R_4 represents the

$$-O-C(=CH_2)-OMe$$

group, and subjecting the reaction product obtained to a Claisen rearrangement.

5. A process according to claim 4, wherein the reaction is carried out using orthoacetic acid ethyl ester.

6. A process according to claim 4, wherein the reaction is carried out using 1 - dimethylamino - 1,1 - dimethoxy - ethane.

7. A process according to claim 4, wherein the reaction is carried out using ethyl-vinyl ether.

8. A process according to claim 4, wherein the reaction is carried out using tert.-butyl-dimethyl - silyl chloride.

9. A process according to claim 4 and claim 5, wherein 1 - tert.butoxy - 2(R) - methyl-hept - 5(cis) - en - 4(S) - ol is reacted to yield 8 - tert.butoxy - 3(R),7(R) - dimethyl-oct - 4(trans) - en - 1 - oic acid ethyl ester.

10. A process for the manufacture of the carbonyl compounds of formula I given in claim 1, substantially as hereinbefore described with reference to Example 1.

11. Carbonyl compounds of formula I given in claim 1, when manufactured by the process claimed in any one of claims 4 to 10 inclusive.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1978.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.